organelles (Haft, supra). Sorting nexin 5 binds to the Fanconi anemia complementation group A protein (Otsuki, T. et al. (1999) Biochem. Biophys. Res. Commun. 265:630-635).

Sorting nexin-1 (SNX1) is involved in the recognition of lysosomal-targeting motifs. This sorting nexin was originally identified by homology to Saccharomyces cerevisiae Mvp1, a protein involved in sorting proteins destined for localization to the vacuole away from proteins destined for delivery to the cell surface (Ekena, K. and Stevens, T.H. (1995) Mol. Cell. Biol. 15:1671-1678; Kurten, R.C. et al. (1996) Science 272:1008-1010). Molecules targeted for the lysosome that require SNX1 include the carboxypeptidase Y sorting receptor and the EGF receptor. In the absence of SNX1, these molecules become mislocalized (Kurten, supra; Horazdovsky, B.F. et al. (1997) Mol. Biol. Cell 8:1529-1541). A Saccharomyces cerevisiae homolog of SNX1, Vps5, is involved in localizing specific membrane proteins, including the carboxypeptidase Y sorting receptor Vps10, to the Golgi. Vps5 null mutants exhibit defects in vacuolar morphology (Horazdovsky, supra; Nothwehr, S.F. and A.E. Hindes (1997) J. Cell Sci. 110:1063-1072).

The PX domain found in sorting nexins is also found in a variety of other proteins, including the PhoX components of NADPH oxidase and the Cpk class of phosphatidylinositol 3-kinase. Most PX domains contain a polyproline motif which is characteristic of SH3 domain-binding proteins (Ponting, supra). SH3 domain-mediated interactions involving the PhoX components of NADPH oxidase play a role in the formation of the NADPH oxidase multi-protein complex (Leto, T.L. et a. (1994) Proc. Natl. Acad. Sci. USA 91:10650-10654; Wilson, L. et al. (1997) Inflamm. Res. 46:265-271). The PX domain is just one example of a domain specialized for promoting protein-protein interactions. Further examples of protein-protein interaction domains are discussed below.

The SH3 domain is defined by homology to a region of the proto-oncogene c-Src, a cytoplasmic protein tyrosine kinase. SH3 is a small domain of 50 to 60 amino acids that interacts with proline-rich polypeptide ligands. SH3 domains are found in a variety of eukaryotic proteins involved in signal transduction, cell polarization, and membrane-cytoskeleton interactions. In some cases, SH3 domain-containing proteins interact directly with receptor tyrosine kinases. The structure of SH3 is characterized by two antiparallel beta sheets packed against each other at right angles. This packing forms a hydrophobic pocket lined with residues that are highly conserved between different SH3 domains. This pocket makes critical hydrophobic contacts with proline residues in the polypeptide ligand (Feng, S. et al. (1994) Science 266: 1241-1247).

A novel domain, called the WW domain, resembles the SH3 domain in its ability to bind proline-rich ligands. This domain was originally discovered in dystrophin, a cytoskeletal protein with direct involvement in Duchenne muscular dystrophy (Bork, P. and M. Sudol (1994) Trends Biochem. Sci. 19:531-533). WW domains have since been discovered in a variety of intracellular signaling molecules involved in development, cell differentiation, and cell proliferation. The structure of the